Clinical Endocrinology (2015) **83**, 157–161 doi: 10.1111/cen.12730

CLINICAL QUESTION

What is the optimal bone-preserving strategy for patients with Addison's disease?

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Summary

Addison's disease is associated with low bone mineral density and increased risk of hip fractures. Causes are multifactorial, contributed by underlying adrenocortical hormonal deficiency, associated autoimmune endocrinopathies, electrolyte disturbances and, in some patients, supraphysiologic glucocorticoid replacement. Recent realization of physiologic cortisol production rate has revised downwards glucocorticoid replacement dosages. Meanwhile, new research has emerged suggesting complex interplay between sodium and calcium homoeostasis under the influence of mineralocorticoid and parathyroid hormone that may impact bone health. As the prevalence of Addison's disease is rising, and osteoporosis and fractures are associated with significant morbidity and increased mortality, attention to bone preservation in Addison's disease is of clinical relevance and importance. We suggest an approach to bone health in Addison's disease integrating physiologic adrenocortical hormonal replacement with electrolyte and mineral homoeostasis optimization.

(Received 14 December 2014; returned for revision 14 January 2015; finally revised 16 January 2015; accepted 26 January 2015)

Introduction

Addison's disease (AD) is characterized by primary cortical hypofunction, resulting in a deficiency of mineralocorticoid (MC), glucocorticoid (GC) and adrenal androgens. Skeletal integrity is dependent not only on the parathyroid hormone (PTH)–vitamin D–calcium axis, but also on the interplay between renin–angiotensin–aldosterone, GC and sex steroid systems in the context of whole-body mineral homoeostasis. Significant perturbations of these axes occur in AD, and strategies in ameliorating hypoadrenal symptoms are topical research subjects. A less well-recognized management issue is bone health preservation. Both hypoadrenalism and suboptimal hormone replacement are associated with bone loss and/or fractures. Superimposed on bone loss are AD-related autoimmune endocrinopathies and heighted fall risks, which perpetuate fracture hazards. These issues pose challenges in AD bone health management.

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Case

A 57-year-old woman with a history of AD and hypothyroidism presented for osteoporosis evaluation. Bone mineral density (BMD) measurement of femoral neck and spine revealed T-scores of −1·9 SD and −2·2 SD; Z-scores of −1·4 SD and −1·9 SD, respectively. Medications included hydrocortisone thrice daily (10/4/4 mg), fludrocortisone 0·1 mg daily, thyroxine 100 μg daily and vitamin D_3 25 μg daily. The patient was clinically euvoluaemic and blood pressure was 125/75 mmHg with no postural changes. Biochemistry revealed hyponatraemia 132 mmol/l, otherwise normal electrolytes and thyroid function. Plasma renin activity was 4·2 nmol/l/h (normal range 1–3·5); 25-OH vitamin D level was 45 nmol/l.

Is BMD low in patients with Addison's disease?

Figure S1 summarizes published results stratified to gender and BMD sites. Most studies found reduced mean BMD by Z-scores but were underpowered to determine significance of effects. The largest study including 292 patients with AD from Norway, the United Kingdom and New Zealand found significantly reduced femoral neck and spine BMD Z-scores.[1] Based on T-score criteria from World Health Organisation, more than 50% of AD patients had osteopenia and up to one in five patients had osteoporosis.[2,3]

Is fracture risk increased in Addison's disease?

Only one study has examined the risk of fractures in AD. Among 3129 patients in a population study, the risk of hip fracture was nearly twofold greater in patients with AD compared to age- and gender-matched controls.[4] The highest risk of fracture was seen in the year before and the year after AD diagnosis,

suggesting excess risk may be related to both pre- and postdiagnosis factors.

What are the risk factors for osteoporosis and fractures in Addison's disease?

Aetiologies of bone loss/fractures are multifactorial. Both hormonal deficiencies and therapies could play contributory roles. Fig. 1 illustrates interacting hormonal/therapy-related risk factors for bone loss, falls and fractures in AD, which are discussed below.

Prediagnosis: factors intrinsic to adrenocortical failure

GC is essential for osteoblast differentiation, and cortisol deficiency results in osteoblast immaturity and lower bone mass.[5] Sex steroids are bone anabolic. Adrenal androgens, including dehydroepiandrosterone (DHEA), DHEA sulphate and androstenedione, are converted into testosterone intra-adrenally and peripherally, which upon aromatization yield oestradiol. Circulating testosterone and oestradiol levels correlate positively with BMD in both genders.[6] Adrenal-derived androgens contribute up to 65% of testosterone in women and 5% in men. As a result, postmenopausal patients with AD or those with concurrent hypogonadism are at higher risk of androgen deficiency-related bone loss. Furthermore, falls are a strong risk factor of fractures. To our knowledge, no studies have examined fall risk in patients with AD. Muscle weakness and postural instability arising from hyponatraemia and/or androgen deficiency are theoretical risk factors for falls in patients with AD.

Postdiagnosis – factors related to hormone replacement

GC replacement. GC excess accelerates bone loss, induces myopathy and increases fracture risks. GC over-replacement is a well-recognized cause of osteoporosis. Previous GC replacement regimens frequently approached 30 mg hydrocortisone equivalent per day, exceeding normal daily cortisol production nearly threefold. To minimize osteoporosis risk, conventional GC replacement has been revised to approximate 20 mg hydrocortisone equivalent per day (0·2–0·3 mg/kg).[7] Indeed, BMD in patients with AD treated with approximately 20 mg daily had better preserved Z-scores compared to those on >30 mg daily.[8] In addition to GC dosage, a common polymorphism in the efflux transporter P-glycoprotein is associated with reduced bone mass,[1] suggesting pharmacogenetics could further modulate susceptibility to GC-induced bone loss in patients with AD.

MC replacement. MC over-replacement causes fluid retention and oedema. However, potential impact of MC over-replacement on bone has only been appreciated recently through assessment of bone status in patients with primary hyperaldosteronism. Excess aldosterone is associated with osteoporosis and vertebral fractures.[9] The risk of osteoporosis was 2–3 times higher in patients with MC excess compared to controls.[9,10] This may be partly related to hypercalciuria and secondary hyperparathyroidism, because sodium/calcium transport is coupled in the nephron, and relative MC excess results in sodium retention that overwhelms calcium reabsorptive capacity. Whether excess MC treatment compromises bone heath in AD has not been investigated.

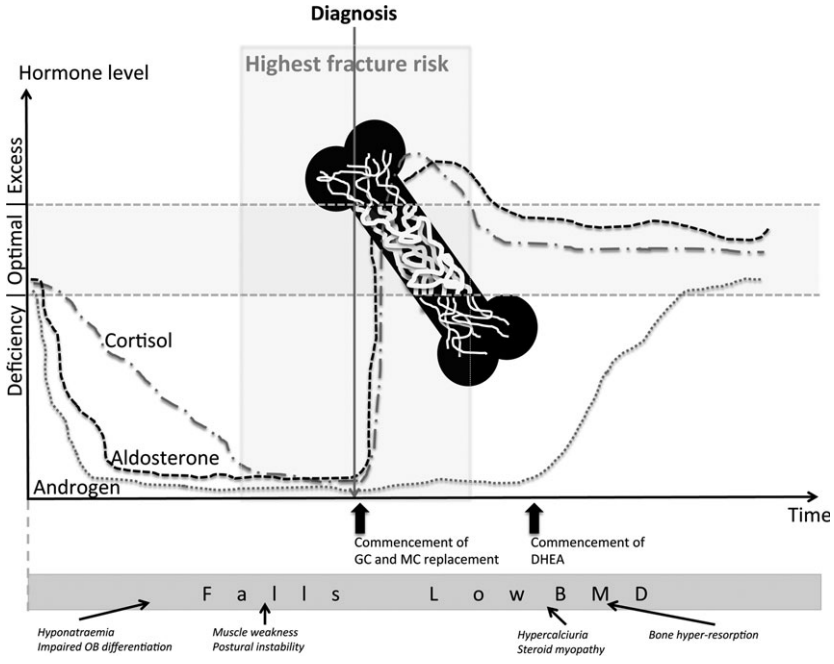

Fig. 1 Schematic diagram depicting risk factors for bone loss and fractures among patients with Addison's disease. Deficiency of adrenocortical hormones impairs osteoblast (OB) differentiation, muscle function and hyponatraemia/dehydration increase fall risks prediagnosis. Immediately postdiagnosis, risk of fracture remains high possibly because of potential electrolyte instability and initial high-dose therapeutic glucocorticoid (GC) regimes, in the setting of 'return to physical activity' in symptomatically much improved patients. Long-term bone loss is related to supraphysiologic glucocorticoid, androgen deficiency and/or hypercalciuria. BMD, bone mineral density; MC, mineralocorticoid; DHEA, dehydroepiandrosterone.

The hazards of potential over GC and/or MC replacement lead to a clinical conundrum because insufficient replacement of either hormone also impairs bone health [see *prediagnosis*]. GC and MC insufficiency result in volume contraction, salt losing, excess antidiuretic hormone secretion and hyponatraemia. The implication of hyponatraemia on mineral homoeostasis, even if mild (130–135 mmol/l), is suggested by studies linking hyponatraemia to osteoporosis[11] and fractures.[12] The risk of fractures is increased threefold among hyponatraemic patients independent of BMD.[12] Animal studies suggest bone loss to arise from compensatory bone resorption to release osteoid sodium to replete circulating sodium.[13] Although it is not known whether the same risk can be extrapolated to hyponatraemic patients with AD, hyponatraemia in AD in theory could trigger similar bone compensation. Hyponatraemic patients are also at increased risk of falls.[14] Up to 15% of patients with AD reported dizziness in one study,[15] and postural instability may contribute to excess falls and fractures.

Androgen replacement. Some,[16,17] but not all,[18–23] studies showed significantly reduced Z-scores in men; while Z-score was lower in women in three studies,[18–20] but not others.[16,17,21,22] BMD levels were the lowest in hypogonadal men[17] and postmenopausal women,[18,20] suggesting possible modulatory role of sex steroids on bone status. Indeed, androgen replacement, in the form of DHEA, reversed bone loss at femoral neck in a 12-month randomized placebo-controlled study of over 100 patients with AD.[2] Collectively, these results suggest androgen deficiency further exacerbates bone loss in AD, a consequence reversible by DHEA replacement.

Do associated autoimmunopathies contribute to bone loss in Addison's disease?

Prevalence of autoimmune comorbidities are approximately 66–73% in AD, especially hypothyroidism and pernicious anaemia.[3,15] Vitamin B_{12} deficiency is associated with both an increased risk of osteoporosis as well as hip and spine fractures.[24] Premature ovarian failure poses additional risk of bone loss from androgen deficiency. Unrecognized concomitant deficiency of these hormones may compromise energy level and compound fall risks.

Management of bone health in Addison's disease

The prevalence of AD approaches 140 cases per million people and its incidence is rising in some countries.[3,25,26] Osteoporosis and fractures are associated with increased morbidity and mortality. Careful evaluation of bone status for its optimization should be integrated into routine care of patients with AD. We hereof propose an assessment and treatment algorithm to optimize bone preservation in AD (Fig. 2).

Step 1: Calcium/vitamin D status optimization

No specific guidelines exist for calcium/vitamin D supplementation in AD. While a current standard of osteoporosis treatment, calcium/vitamin D supplementation may be overlooked in the complex medical management of patients with AD. Total daily calcium intake (dietary source and supplementation combined) should target 1000–1200 mg,[27] and a serum 25-hydroxyvitamin D level of >75 nmol/l is desirable.[28] Hypothyroidism and coeliac disease are not infrequent comorbid autoimmune conditions in AD. Attention to timing/dosage of calcium and thyroxine is important to ensure adequate absorption.

Step 2: GC/MC dosages optimization

As Fig. 1 illustrates, excess or under replacement of GC and/or MC can both lead to bone loss. We aimed for 0·2–0·3 mg/kg hydrocortisone equivalent daily. Fludrocortisone dosage typically varies between 0·1 and 0·3 mg daily, and dosage may be lower when hydrocortisone is used (20 mg daily equivalent to 0·1 mg fludrocortisone MC activity). The goal was eunatraemia and plasma renin at the upper limit of normal. Although one should be guided by clinical picture, it is conventional practice to increase the fludrocortisone dose if renin remains high. Care should be taken not to oversuppress renin as it may result in hypercalciuria and eventual bone loss. On the other hand, relative hyper-reninaemia results in natriuresis, induces negative sodium balance and may increased risk of hyponatraemia-induced osteoporosis. In patients with elevated plasma parathyroid hormone levels, 24-h urinary calcium excretion should be measured to exclude hypercalciuria that could help guide MC replacement dosage in selected osteopaenic patients.

Step 3: Selective use of androgen

Selected patients with ongoing suboptimal energy level despite optimal GC and MC replacement, especially women with low adrenal androgen levels and symptoms of androgen deficiency, such as low libido, may be candidates for DHEA replacement.

Step 4: Fracture risk stratification

As bone loss may precede clinical AD diagnosis (Fig. 1), patients with AD should be assessed for risk of osteoporosis, especially those with additional risk factors such as vitamin D deficiency. BMD measurement is indicated among patients with history of minimal trauma fractures and/or concomitant gonadal failure. BMD measurement at diagnosis may serve as a comparative baseline valuable for future monitoring. Given spine BMD reduction tends to be greater than the hip (Figure S1), thoracolumbar X-ray is useful for further risk stratification based on the presence/absence of asymptomatic fractures. Antiresorptive therapies may be considered among patients at high risk of future fracture and may be estimated by Fracture Risk Assessment Tool (FRAX),[29] if available.

Back to the patient

Thoracolumbar X-ray showed no fractures. The patient reported suboptimal energy level and poor libido. DHEA sulphate level

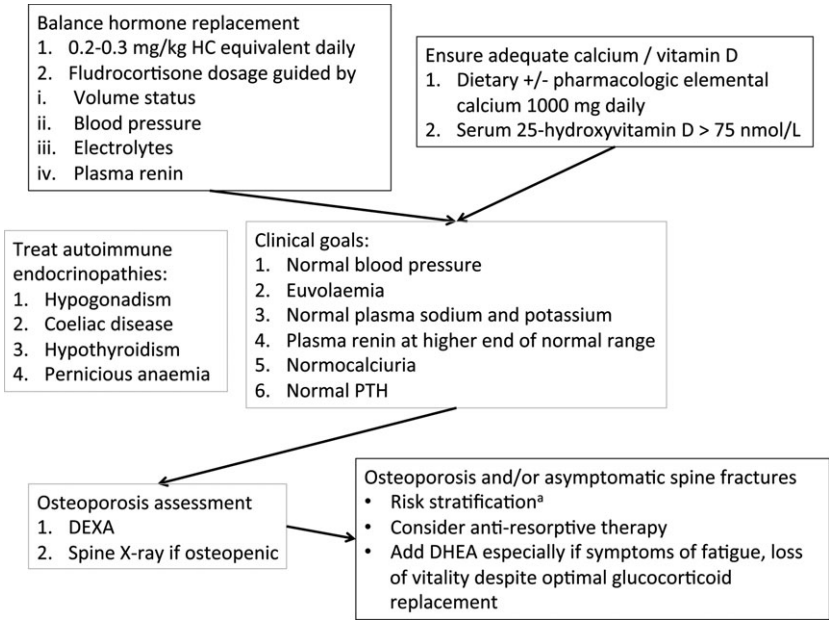

Fig. 2 Suggested bone health management algorithm for patients with Addison's disease. HC, hydrocortisone; PTH, parathyroid hormone; DEXA, dual-energy X-ray absorptiometry; DHEA, dehydroepiandrosterone; [a]fracture risk may be estimated by Fracture Risk Assessment Tool (FRAX).[29]

was undetectable. Coeliac disease serology was negative. Vitamin D insufficiency, androgen deficiency and possibly hyponatraemia from fludrocortisone under-dosage were considered contributing factors to osteopenia. Vitamin D_3 was increased to 50 ug daily and fludrocortisone to 0·15 mg daily. DHEA 25 mg daily was commenced. Repeat biochemistry 6 months later showed normalization of serum sodium, reduction of plasma renin activity to 3·2 nmol/l/h and rise of 25-hydroxyvitamin D level to 72 nmol/l. Parathyroid hormone and 24-h urinary calcium excretion were within normal limits. DHEA sulphate level had risen to 7·7 μmol/l (normal range: 3–12). BMD measurement 12 months later showed stable levels in the spine and femoral neck.

Conclusion

Data from the past 10–15 years have shown that morbidity remains high, and life expectancy is reduced among patients with AD.[30] The challenges of AD management include not only adrenal crises prevention, but also maintenance of long-term cardiometabolic health. Bone preservation is sometimes neglected in the midst of complex medical management of AD, but it is important in the prevention of fractures, which are associated with significant morbidity and mortality. This entails optimization of GC and MC replacement regimes, minimization of hyponatraemia and avoidance of hypercalciuria, maintenance of calcium/vitamin D sufficiency, as well as selective use of androgen replacement.

Acknowledgements

PL is supported by an Early Career Fellowship of the NHMRC, Australia and the Fellows Research Establishment Fellowship of the Foundations, Royal Australasian College of Physicians. JGR is the recipient of the Don Chisholm Fellowship (funds from Garvan Research Foundation, including support from GlaxoSmithKline, Australia, Diabetes Australia Research Trust, the Commonwealth Department of Health and Ageing).

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